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July 8, 2002

Dr. Michael Shelby
CERHR Director
NIEHS
79 T.W. Alexander Drive
Building 4401, Room 103
P.O. Box 12233
MD EC-32
Research Triangle Park, NC 27709

Re: Written Comments on April 2002 Methanol Expert Panel Report

Dear Dr. Shelby:

The American Forest & Paper Association (AF&PA) submits the following comments in response to the NTP Center for Evaluation of Risks to Human Reproduction's May 8, 2002 request for comments on the NTP-CERHR Expert Panel Report on the Developmental and Reproductive Toxicity of Methanol (the "Report"), 67 Fed. Reg. 30,942. AF&PA is the national trade association of the forest, paper, and wood products industry. AF&PA represents more than 300 member companies and related trade associations involved in growing, harvesting, and processing wood and wood fiber; manufacturing pulp, paper, and paperboard from both virgin and recycled fiber; and producing solid wood products.

AF&PA has a substantial interest in the assessment of risks presented by exposure to methanol, because naturally occurring methanol is released during the manufacture of wood products and wood pulp. AF&PA previously submitted comments, dated September 7, 2001 and January 11, 2002, on a draft of the Report. Forest products industry consultants offered oral comments during the Methanol Expert Panel's meeting on October 15-17, 2001. AF&PA also responded, on October 2, 2000, to CERHR's August 17, 2000 request for data to be reviewed by the Methanol Expert Panel.

AF&PA submitted extensive analysis of the potential for exposure to methanol emissions to create risks to human health and the environment, including adverse effects on human reproduction and development, in connection with its March 8, 1996 petition to EPA to remove methanol from the list of "hazardous air pollutants" under the Clean Air Act. Those materials were also provided to CERHR in AF&PA's October 2, 2000 submission. AF&PA strongly believes that this information, along with the additional information presented in the Report and in AF&PA's oral and written comments on the draft Report, demonstrates that sufficient data are

available to conclude there is no significant risk of adverse effects on human reproduction and development from exposure to methanol via air pollution.

AF&PA believes that the information it previously provided contains important analyses that the Expert Panel needed to consider, and in fact the Report reflects consideration of some, but not all, of the points contained in AF&PA's analysis. The following comments suggest several areas in which AF&PA believes the Report should be modified to make additional or more accurate reference to the materials AF&PA has provided. In addition, a key expert analysis of the statistical significance of results reported in the principal methanol study in primates, prepared by Dr. David Hoel and submitted to CERHR on January 11, 2002, apparently was too late to be considered by the Panel, and this letter addresses the critical findings of that statistical analysis.

AF&PA urges the NTP staff to address these and other comments on the Report and issue a final NTP report promptly. Because methanol is widely used and is released to the environment in large quantities, accurate, comprehensive, peer-reviewed information on methanol's developmental and reproductive toxicity will be valuable to many parties. Moreover, EPA apparently is now relying in other contexts on the unrealistic assessment of methanol's developmental and reproductive toxicity contained in its denial of AF&PA's petition to remove methanol from the hazardous air pollutants list. That risk assessment concluded that methanol may cause reproductive or developmental effects at concentrations as low as 0.3 mg/m^3, which in turn would increase blood methanol concentration by only 0.006 mg/l (compared to a mean concentration from natural metabolism and diet of 1.8 mg/l and a standard deviation of around 0.7 mg/l).

Need to Recast Discussion of Developmental Toxicity in Light of Burbacher Study

The Report's discussion of the Burbacher study, sponsored by the Health Effects Institute (HEI), on methanol disposition and reproductive toxicity in adult females and offspring developmental effects following maternal inhalation exposure (References 52 and 143 of the Report), fails adequately to consider the limitations and shortcomings of the statistical analysis of the study. AF&PA believes that the Burbacher study does have substantial value for the Expert Panel's task, but that value is that the Burbacher study is a comprehensive assessment of the reproductive and developmental toxicity of maternal methanol inhalation which shows no meaningful adverse effects for exposures as high as 1800 ppm.

The Burbacher study itself, and especially the included HEI peer-review commentary, present findings that at most suggest areas for further research, rather than confirming any adverse effects on mothers or their offspring from exposure to up to 1800 ppm of methanol. A large number of tests were performed, and yet the analysis of variances showed no statistically significant difference between the control group and the exposed groups in any of these measures of reproductive and developmental toxicity. Only when the researchers performed *post hoc* "linear contrast" comparisons between various groups did any differences emerge. The HEI peer-review panel and AF&PA's experts have all concluded that these analyses could easily

identify apparently differences between controls and exposed animals merely by chance, given the small number of animals, the multitude of tests, and the variability of individual responses.

The statistical analyses in the Burbacher Study present the possibility of misconstruing random fluctuations as effects of methanol exposure. The information that might be used to corroborate statistically identified differences in fact tends to disprove the hypothesized effects. As the HEI peer-review commentary notes and AF&PA's experts stated even more strongly, the lack of clear, monotonic dose-response relationships, despite clear differences in blood methanol concentrations; the lack of consistency among cohorts, sexes, and tests; and the difficulty of explaining apparent effects in the 200 ppm group, where maternal blood methanol was only slightly elevated above background; all undercut any assertion that the study's potentially random events demonstrate an effect of methanol on reproductive or developmental health.

To help EPA understand the significance of Burbacher's observations, AF&PA retained a renowned biostatistician, David G. Hoel. Dr. Hoel has a Ph.D. in Statistics from the University of North Carolina at Chapel Hill. He is currently Distinguished University Professor at the Medical University of South Carolina. Previously he had a long association with the National Institute of Environmental Health Sciences, including serving as its Acting Director and the Director of the Division of Biometry and Risk Assessment. Dr. Hoel has served on numerous National Academy of Sciences committees and other U.S. government advisory committees and serves on the editorial board of numerous publications, including the *Journal of Statistical Computation and Simulation*, the *Journal of Communications in Statistics*, and the *Journal of Environmental Pathology, Toxicology and Oncology*.

The December 30, 2001 report from Dr. Hoel, which AF&PA submitted to CERHR on January 11, 2002, as well as his analyses previously submitted to CERHR by AF&PA, details the shortcomings in the statistical analyses and conclusions of the Burbacher study. Dr. Hoel's work demonstrates, as he stated in his September 7, 2001 written comments to the Panel, that the data generated by Burbacher "provide a good example of how a large number of statistical tests can produce a few inconsistent, but entirely expected, positive results even when the experiment is truly negative. Based on the sheer number of statistical tests that were employed by Burbacher *et al.* and their failure to adequately control the experiment-wide false positive error rate, we are forced to conclude that there is no convincing evidence for an effect of methanol exposure on the behavioral measures evaluated in these primates."

The HEI review panel discussion of the Burbacher study noted concerns about the statistical techniques applied and the failure to adjust for multiple comparisons. The Report itself noted these concerns and stated that "[m]ore insight may be provided by an independent statistical analysis...." (Report at 74.) Most Panel members recommended a reanalysis of the Burbacher study data, stating that a "more rigorous statistical evaluation that adjusts for multiple comparison may permit consensus as to whether there is evidence that methanol is a developmental toxicant in monkeys." (Report at 111.) Dr. Hoel has conducted such an analysis and it was provided to CERHR on January 11, 2002, but apparently it was never reviewed by the Methanol Expert Panel. That analysis requires revision of the Report's statements about the results of the Burbacher study and its significance.

Dr. Hoel has summarized his reanalysis of the Burbacher study data using statistical methods that are optimally matched to the study's experimental design, with appropriate adjustment of the false positive error rate for the multiple comparisons problem. He also performed analyses using non-parametric statistical methodology that is robust to departures from normality and equality of variances, to ensure that such departures do not invalidate any conclusions.

The results of Dr. Hoel's reanalysis of the Burbacher study data are clear-cut and consistent. There were *no* endpoints for which statistically significant effects were observed. Dr. Hoel's overall conclusion, which must also be the conclusion of the NTP staff, is that the Burnacher study "showed no reproductive or offspring developmental effects of methanol exposure." Given that a well-designed study tested many endpoints in a species very relevant for assessing potential toxicity in humans and found no statistically significant effects, even at exposures orders of magnitude higher than what humans are expected to encounter, provides sufficient basis for the final NTP report to conclude that there is minimal concern for reproductive and developmental toxicity from expected human exposure to methanol.

(We also note that the Report contains a statement, at the top of page 97, that is both a *non sequitur* and non-sensical: "Both the rodent and primate neurobehavioral outcomes do suggest alterations in cognitive function are consistent and subtle." The only neurobehavioral adverse effects observed in rodents was in the Weiss single, high-dose (4500 ppm) study--a possible effect in running in a wheel which appeared only when the results were analyzed separately by sex, and perhaps subtle effects in changing patterns of sequential response--which were also subject to the same lack of compensation for multiple testing that plagued the statistical analyses in the Burbacher study. (See Report at 72.) These effects were neither internally consistent, nor consistent with other neurobehavioral assessments in rodents, nor consistent with Burbacher's results in primates. The Burbacher study itself of course did not reveal any statistically significant effects when analyzed correctly, but even the HEI Report suggested that the effects Burbacher noted were not internally consistent (better performance in high dose group, differences between cohorts, inconsistency with other measures of similar functions, etc.). What the rodent and primate studies have in common is that only through multiple comparisons, with failure to adjust the statistical analysis to reflect those multiple comparisons, could subtle, inconsistent effects be coaxed from the data.

An additional point, also not reflected in the Report, is Dr. Hoel's previous analysis showing that the observed effect in the visually directed reaching test could be explained simply by the unusually long mean gestation period of the controls, which in turn was disproportionately affected by a single outlier that was delivered post-maturity. If gestational age rather than age since birth is used to determine how quickly an infant masters the visually directed reaching test, then no effect would be seen in the methanol-exposed group, even applying the statistical tests Burbacher used. An EPA Office of Research and Development scientist who reanalyzed the Burbacher study with that in mind concluded that there was in fact no effect of methanol exposure in that test. (See August 16, 2000 Memorandum from Jeff Gift to Mike Davis, "Comments on AF&PA methanol delisting petition submission dated July 3, 2000," at 3.))

Unwarranted Downplaying of Aspartame Studies

The Report describes extensive studies by Reynolds *et al.* (Reference 147 in the Report) and Suomi (Reference 148), in which aspartame was fed to five groups of monkeys, each group consisting of four monkeys. Because aspartame is hydrolyzed to methanol in the gut, the Rogers and Suomi studies represent exposure of infant monkeys to methanol ranging up to 250-270 mg/kg bw/day. That methanol exposure did not have an effect on growth or numerous developmental milestones, including various measures of learning performance and hearing ability.

The Report somewhat discounts the value of these studies because "the statistical power of the hypothesis tests is unclear," and because "[t]he studies did not find any effects at the doses used" and "the only useful information to come from them is that the highest dose appears to be tolerated." (Report pages 75-76.) As Dr. Hoel pointed out in AF&PA's September 7, 2001 comments, the remarks about the statistical power of the testing apply equally to the Burbacher study; in any event, if this is an important issue the statistical power calculations could be carried out at this point from available data, as Dr. Hoel has for the Burbacher study.

Most important, as Dr. Hoel notes, is that the findings of Reynolds and Suomi are consistent with the findings (properly interpreted) of Burbacher; namely, that both prenatal and neonatal exposure to methanol in doses likely to substantially exceed human exposures do not have an effect on growth or neurobehavioral development. It is perplexing that the Report seems to regard this important finding as a "weakness" or "flaw" of the Reynolds and Suomi studies. AF&PA also suggests that, rather than stating that "the highest dose appears to be tolerated," the report should state that the Reynolds and Suomi studies show that methanol "does not affect learning, hearing ability, and other developmental milestones at the highest dose tested (equivalent to 250-270 mg methanol/kg bw/day)." (In particular, use of the term "tolerated" might be read to mean only that the highest dose was ingested and did not produce acute toxicity.)

The statement that the study "should have continued to higher doses" is perplexing in several ways. First, it appears that this study, which was after all of aspartame, was conducted at the solubility limit of aspartame, and in any event the resulting methanol doses in the two highest aspartame dose groups were considerably higher than anything humans are likely to experience from ambient or occupational exposures to methanol. Second, since this study took place over at least a year and a half, the researchers would have had no way to know during the feeding stage that the highest dose would not produce adverse effects. Third, while this statement is not qualified as being the view of only one Panel member, the following statement ("and, in the view of this Panel member....") suggests that perhaps it is.

Moreover, the suggestion of that one Panel member that the study should have continued to higher doses even "if doing so required alternative routes of administration" is a misplaced criticism. Since, as noted above, the researchers were administering aspartame orally at the limit of its solubility, and in so doing achieved a dose 300 times higher than the estimated 99th percentile aspartame intake for children, diabetics, and women of childbearing age (*cf.* Report at

7), conducting the study at a higher dose by some other route of administration would not have been a relevant exposure for studying the potential effects of using aspartame as a sweetener.

The statement that, although these studies "reasonably rule out the possibility that the aspartame/phenylalanine doses employed have very large effects on the endpoints assessed, but what is unclear is the effect size with which the data are compatible," likewise suggests a preconceived outcome. Reynolds and Suomi conducted an extensive battery of tests and assessments at frequent intervals up to 1 ½ years of age. The implication here that this study would only have uncovered "very large effects" is unwarranted. Rather, the Report should acknowledge that both Burbacher (properly interpreted) and Reynolds and Suomi found no developmental effects in non-human primates at the highest doses tested, which were orders of magnitude higher than anticipated human exposure.

Improper Conclusions on Possible Effect on Gestation Length in Burbacher Study

The Report describes the statements in the Burbacher study that maternal exposure to airborne methanol resulted in reduced gestation length. The Report incorrectly accepts the statement that methanol-exposed groups had about 5% shorter gestation, going on to conclude that this finding is of "uncertain utility" because of four factors which had previously been identified by AF&PA. The Report fails, however, to reflect the true lack of a statistically significant effect on gestation length. (See Report at 73, 104, 106.)

The analyses of the Burbacher study which AF&PA provided to EPA on July 3, 2000 (Reference 166 in the Report) and September 1, 2000 and to CERHR on October 2, 2000 demonstrate that the Burbacher study does not provide sufficient basis to conclude that methanol exposure had any effect on gestation length. First, gestation length for all of the exposed cohorts was within the normal range for *Macaca fascicularis*. Second, the observed reduced gestation length was not accompanied by any other signs of pre-maturity, such as reduced birth weight or reduced head circumference. Third, no dose-response relationship was observed.

Fourth, and most importantly, the observation of reduced gestation length was dictated by the fact that one offspring in the control group had an abnormally long gestation length, accompanied by signs of post-maturity. As explained in AF&PA's July 3, 2000 submissions to EPA, one monkey in the control groups had a duration of pregnancy of 178 days, which was outside the normal range for other colonies of macaques and was more than two standard deviations beyond the observed mean of 167 days for the control group. See, e.g., AF&PA July 3, 2000 submission at 12. The fact that this was an "outlier" is "confirmed" by the fact that the 178-day-gestation infant exhibited signs of post-maturity (meconium staining and hyperemia). See comments of Anthony Scialli, M.D. of Georgetown University School of Medicine, a well-kown expert in reproductive toxicity, included in Reference 166. Dr. Hoel's September 7, 2001 submission and the December 30, 2001 report by Dr. Hoel show that this one outlier in the control group "leads to an invalid inference that the exposed groups' pregnancy durations were significantly shortened by methanol exposure." *Excluding that outlier from the control group results in a conclusion that there was no significant difference in the gestation lengths between the control groups and the exposed groups.* This is a critical finding that the Report curiously

ignored. The Burbacher study thus does not show a possible effect of methanol on duration of pregnancy; it shows that concentrations up to 1800 ppm did not produce a statistically significant change in gestation length (nor in any other reproductive parameters, as the Report already acknowledges).

Finally, Burbacher's observations of reduced gestation length were also influenced by the fact that there were a relatively large number of Cesarean section births (five) in the exposed groups, but none in the control groups. (The C-sections were included in gestation length calculations-- see Burbacher (Reference 52 at p. 45 and Table 17.) Dr. Alice Tarantal, an expert primatologist with a particular expertise in prenatal and neonatal care of primates and especially *Macaca fascicularis*, in her report that AF&PA submitted to EPA on July 3, 2000 (Reference 166 in the Report) and in materials presented to EPA in September 1 (provided to CERHR but not referenced in the Report), observed that spontaneous vaginal bleeding, which apparently triggered the decision to perform Cesarean sections in four of the five cases, is not a reliable indicator of maternal or fetal distress, and therefore the high incidence of Cesarean sections in the exposed groups is "most likely spurious." The observation that "it is noteworthy that C-sections were performed only on methanol-exposed females" (Report at 104) may be confusing cause with effect. It is unclear from Reference 52 whether vaginal bleeding, which is not uncommon, also occurred in the control groups but was not reported. In any event, it would not be surprising for the researchers to conclude that vaginal bleeding in the exposed animals was an indicator of maternal or fetal distress and therefore resort to C-sections in those cases. The Report should have stopped with the observation that no adverse reproductive outcomes (other than the alleged reduced gestation period) were statistically significant.

Thus, in AF&PA's July 3, 2000 submissions to EPA, Dr. Tarantal, Dr. Hoel, and Dr. Scialli all concluded that the Burbacher study does not provide evidence of methanol reproductive toxicity. Dr. Hoel's subsequent statistical analyses reinforce that conclusion and should have been reflected in the Report. For the reasons stated above and in those submissions, AF&PA disagrees with the conclusion in the Report that the data are insufficient to assess effects of methanol on parturition in primates." (Report at 106; see also 104.) Rather, it appears that there are relatively extensive data on reproductive effects in rodents and confirmatory data from Burbacher on reproductive effects in non-human primates, which failed to find an effect that was either statistically significant or dose-related.

Confusion in the Report About the Toxic Agent and Implications for Subpopulations

The Report states (correctly, in AF&PA 's view) that methanol blood level is "a useful biomarker of exposure and effect" and that "methanol *per se* is the likely developmental toxicant in mice." (See Report at 92.) Moreover, to the extent that any dose-response relationships have been demonstrated with developmental or reproductive effects, they have been with methanol exposure and blood methanol levels, rather than formate levels. (At the low concentrations to which humans may be exposed, the methanol metabolic pathway is not even near saturation.) The Burbacher study included extensive monitoring of pregnant females and found no formate accumulation resulting from methanol exposures of up to 1800 ppm (Reference 52 at 40-42),

belying any suggestion that the effects reported there could be the result of formate accumulation rather than methanol.

Yet in numerous places, the Report makes statements or expresses reservations that are inconsistent with those conclusions. For example, although Burbacher reported no difference in methanol absorption and metabolism in pregnant monkeys (Reference 52 at 37-40), the Report expresses concern because the Burbacher study "does not address the issue of susceptibility due to folate deficiency." (Report at 75.) If methanol is the toxic agent presumed to have the potential to cause developmental or reproductive effects, then it is the methanol that monkeys (or humans) will be exposed to in their bloodstream, and not the varying levels of formate that may accumulate, as varying levels of folate affect the metabolism of formate, and not the metabolism of methanol. The same can be said of the Report's suggestion (p. 63) that "women of low folate status may be more susceptible to the adverse developmental effects of methanol." Folate deficiency, at least for the methanol exposures at issue here, would affect formate accumulation, not methanol accumulation.

The Report should be consistent. Recognizing that blood methanol is a useful biomarker of exposure and effect and that methanol is the likely developmental toxicant in mice, the Report should not then go on to speculate, without any justification, that, for example, formate accumulation in folate-deficient pregnant women could cause the developmental effects observed at high blood methanol levels in mice (or incorrectly attributed to methanol exposure in monkeys).

Need to Take Advantage of Pharmacokinetic Modeling

AF&PA's September 7, 2001 comments to CERHR contained a report of the same date by Dr. Thomas Starr, which pointed out a number of ways in which the Draft Report failed accurately to describe or properly utilize PBPK models of methanol in rodents and primates, including humans, by Perkins *et al.* and Horton *et al.* Dr. Starr has over 30 years experience in the field of toxicology and risk assessment, and he is currently a consultant in risk assessment and an adjunct associate professor in the Department of Environmental Sciences and Engineering at University of North Carolina at Chapel Hill School of Public Health. Dr. Starr is a former president of the Society for Risk Analysis and the Risk Assessment Specialty Section of the Society of Toxicology, and he has served on advisory boards to EPA, Duke University, and the State of North Carolina. He has over 70 publications on human and environmental health effects of exposure to pollutants and other toxic substances. AF&PA urges the NTP staff to consider Dr. Starr's comments carefully, as (1) there is a substantial amount of pharmacokinetic information available on methanol and (2) that information can be critical in the evaluation of potential health risks from methanol exposure.

Importantly, Dr. Starr points out that both the Perkins model and, to an even greater extent, the Horton model do a good job of predicting human blood methanol concentrations resulting from exposure to airborne methanol at the concentrations likely to be relevant for the NTP-CERHR risk assessment. Data are available on changes in blood methanol concentration as a result of human exposure to known concentrations of airborne methanol, in several studies.

Those experimental results agree quite well with the PBPK models' predictions of resulting blood methanol concentrations. This information is particularly important (1) for comparing potential effects on humans to experimental effects in rats and mice and (2) for assessing whether changes in human blood methanol that would result from environmental exposures to methanol are biologically relevant (in comparison to endogenous generation and retention of methanol through human metabolism).

The Report acknowledges that pharmacokinetic modeling may be useful for methanol risk assessment, but then says that "such modeling was outside the scope of this Panel." (Report at 47.) (Indeed, AF&PA commented unsuccessfully when the Panel was being formed that modeling experts needed to be included.) In any case, it is very important that the NTP staff preparing the final NTP-CERHR report consider carefully the utility and implications of these models. (And again, suggestions that the models are insufficient because they do not address fetal pharmacokinetics or sensitive subpopulations need to be regarded in light of the known metabolic pathway for methanol, which is nowhere near saturated at the concentrations relevant for humans.)

Inappropriate References to Benchmark Doses

The Report presents "benchmark dose" estimates for the developmental toxicity effects reported in Rogers, *et al.* (Report at page 57.) As explained in Dr. Starr's September 7, 2001 report, it would be inappropriate for the Expert Panel to rely on benchmark dose estimates from the Rogers study in reaching conclusions about methanol developmental toxicity. First, the published report of the Rogers study fails to provide critical information needed to independently replicate (or modify) their model-fitting process and subsequent benchmark dose derivations. Second, the lower-bound benchmark dose estimates presented in the Report are in fact the lower 95% confidence bound estimates of the dose that would pose a 5% added risk (the $BMDL_{05}$). Use of this measure could introduce a substantial, unnecessary additional element of conservatism into the risk assessment process. This lower-bound benchmark dose estimate is necessarily substantially lower than the corresponding NOAEL derived from the same data. (The Report claims that the 95% lower bound estimate of the BMD_{05} "is generally consistent with NOAELs" (Report at 65), but in fact it is almost three times less than the NOAEL for the critical endpoint, cervical rib malformation (Report at 66).)

Furthermore, no justification is offered for setting forth a $BMDL_{05}$, rather than the considerably higher $BMDL_{10}$. EPA's draft benchmark dose methodology recommends using the $BMDL_{10}$ as a surrogate for the NOAEL, rather than the $BMDL_{05}$, for test data that are not "continuous" (a continuous response being on a continuum, e.g., weight loss or head circumference). (EPA, Benchmark Dose Technical Guidance Document (External Review Draft October 2000) at 19, 33, 36, 73, 82.) Since the Report states that modeling was outside the scope of the Panel (Report at 47), the Panel's references to the BMD model must be carefully reviewed.

For these reasons, the benchmark dose estimates contained in the Report would not be an appropriate basis for a reference concentration or a reference dose for humans.

Methanol Blood Concentrations Higher than 10 mg/l Should Be of Minimal Concern in Humans

The Report states that the Panel has "minimal concern" that methanol exposures resulting in less that 10 mg/l blood methanol concentrations may result in developmental toxicity in humans. Based on the information in the Report and the comments provided above, however, there should be minimal concern about substantially higher blood methanol concentrations. As Table 3-8 of the Report (p. 96) demonstrates dramatically, reputed developmental or reproductive effects were only observed in rodents after the animals had been pushed to very high blood methanol concentrations: 537 mg/l in the Rogers study and 1840-2240 mg/l in the Nelson study. The NTP-CERHR report should identify a higher concentration than 10 mg/l, or at least state that human blood methanol concentrations are unlikely to exceed that level except from intention or accidental ingestion of methanol, and therefore anticipated human exposures are of minimal concern.

AF&PA hopes that these comments will be useful to the NTP staff as it completes this important work. We urge NTP-CERHR to complete the NTP-CERHR report on methanol, based on the Methanol Expert Panel Report, promptly, as there is significant interest in this subject, and moreover we believe that the Report contains some inaccurate or incomplete statements that should be corrected promptly. Please contact the undersigned with any questions at (202) 463-2587, fax (202) 463-2423, or john_festa@afandpa.org.

Sincerely,

John L. Festa JLF

John L. Festa, Ph.D.
Senior Scientist